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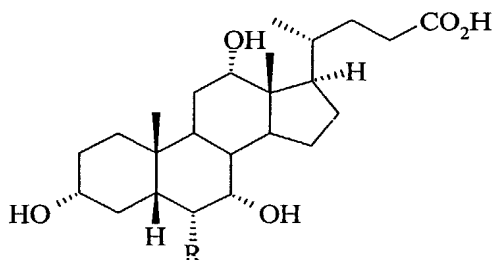
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(54) Title: CHEMICAL COMPOUNDS



(I)

(57) Abstract: The invention relates to compounds of formula (I), wherein R is ethyl, propyl or allyl, and to salts, solvates and pharmaceutically acceptable amino acid conjugates thereof. The compounds of formula (I) are useful as FXR agonists.



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## **CHEMICAL COMPOUNDS**

### **FIELD OF INVENTION**

The present invention relates to farnesoid X receptors (FXR). More particularly, the present invention relates to compounds useful as FXR agonists, to pharmaceutical formulations containing them and to the  
5 therapeutic use thereof.

### **BACKGROUND OF THE INVENTION**

Farnesoid X Receptor (FXR) is an orphan nuclear receptor, identified for the first time from a rat liver cDNA library (BM. Forman, et al., *Cell* **81**:687-693 (1995)) and most closely related to the insect ecdysone receptor.  
10 FXR is a member of the nuclear receptor family of ligand-activated transcription factors that includes steroid, retinoid, and thyroid hormone receptors (DJ. Mangelsdorf, et al., *Cell* **83**:841-850 (1995)). Northern and *in situ* analysis show that FXR is most abundantly expressed in the liver, intestine, kidney, and adrenal gland (BM. Forman, et al., *Cell* **81**:687-693  
15 (1995) and W. Seol, et al., *Mol. Endocrinol.* **9**:72-85 (1995)). FXR binds to DNA as a heterodimer with the 9-cis retinoic acid receptor (RXR). The FXR/RXR heterodimer preferentially binds to response elements composed of two half sites of the nuclear receptor of the consensus sequence AG(G/T)TCA, organized as an inverted repeat and separated by a single nucleotide (IR-1  
20 motif) (BM. Forman, et al., *Cell* **81**:687-693 (1995)). An early report showed that rat FXR is activated by micromolar concentrations of farnesoids such as farnesol and juvenile hormone (BM. Forman, et al., *Cell* **81**:687-693 (1995)). However, these compounds failed to activate the mouse and human FXR, leaving the nature of the endogenous FXR ligand in doubt. Several naturally-  
25 occurring bile acids bind to and activate FXR at physiological concentrations (PCT WO 00/37077, published on 29 June 2000)). As discussed therein, the

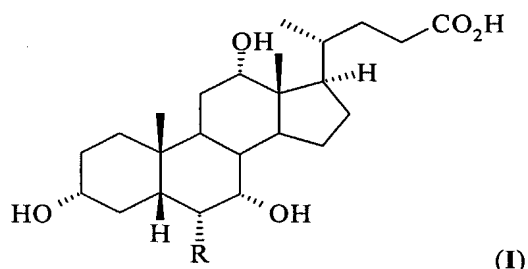
bile acids that serve as FXR ligands include chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), and their taurine and glycine conjugates.

Bile acids are cholesterol metabolites formed in the liver and secreted into the duodenum, where they play important roles in the solubilization and absorption of dietary lipids and vitamins. Most bile acids (~95%) are subsequently reabsorbed in the ileum and returned to the liver via the enterohepatic circulatory system. The conversion of cholesterol to bile acids in the liver is under feedback regulation: bile acids down-regulate the transcription of cytochrome P450 7a (CYP7a), which encodes the enzyme that catalyzes the rate limiting step in bile acids biosynthesis. There are data suggesting that FXR is involved in the repression of CYP7a expression by bile acids, although the precise mechanism remains unclear (DW. Russell, *Cell* 97:539-542 (1999)). In the ileum, bile acids induce the expression of the intestinal bile acid binding protein (IBABP), a cytoplasmic protein that binds bile acids with high affinity and may be involved in their cellular uptake and trafficking. Two research groups have demonstrated that bile acids mediate their effects on IBABP expression through activation of FXR, which binds to an IR-1-type response element that is conserved in the human, rat, and mouse IBABP gene promoters (14; 17). Thus, FXR is involved both in the stimulation (IBABP) and in the repression (CYP7a) of target genes involved in bile acid and cholesterol homeostasis.

European Patent No. 0 312 867, published on 05 May 1992 to Gipharmex S.p.A. discloses 6-methyl derivatives of natural biliary acids such as ursodeoxycholic,ursocholic, chenodeoxycholic and cholic acid.

#### **BRIEF SUMMARY OF THE INVENTION**

According to a first aspect, the present invention provides compounds of formula (I):



(I)

wherein R is ethyl, propyl or allyl, and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof. In one preferred embodiment, the compounds of formula (I) are in the form of the glycine or taurine conjugates.

In another aspect, the present invention provides  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -ethyl- $5\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

10 In another aspect, the present invention provides  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -propyl- $5\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

In another aspect, the present invention provides  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -allyl- $5\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

15 In another aspect, the present invention provides compounds which are FXR agonists.

In another aspect, the present invention provides a pharmaceutical formulation comprising a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

20 In another aspect, the present invention provides a method for the prevention or treatment of an FXR-mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of

formula (I) for the preparation of a medicament for the prevention or treatment of an FXR-mediated disease or condition.

In another aspect, the present invention provides a method for the prevention or treatment of cardiovascular diseases. The method comprises  
5 administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for the prevention or treatment of cardiovascular diseases. In one embodiment, the cardiovascular disease is atherosclerosis.

10 In another aspect, the present invention provides a method for increasing HDL cholesterol. The method comprises administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for increasing HDL-cholesterol.

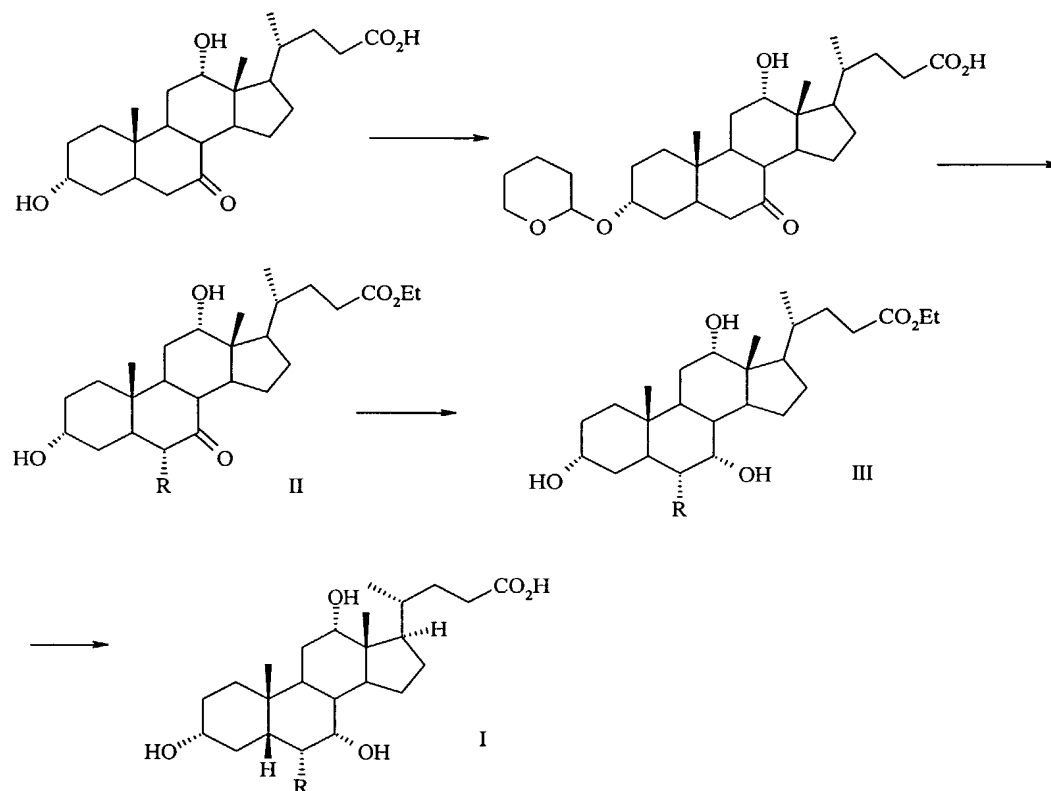
15 In another aspect, the present invention provides a method for lowering triglycerides. The method comprises administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for lowering triglycerides.

20 In another aspect, the present invention provides a method for the prevention or treatment of cholestatic liver diseases. The method comprises administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for the prevention or treatment of  
25 cholestatic liver diseases.

In another aspect, the present invention provides a radiolabeled compound of formula (I). In one embodiment, the compound of formula (I) is tritiated.

The compounds of the invention can be prepared according to any conventional organic chemistry methods. In another aspect, the present invention provides a process for the preparation of a compound of formula (I) as illustrated in scheme 1:

5

**Scheme 1**

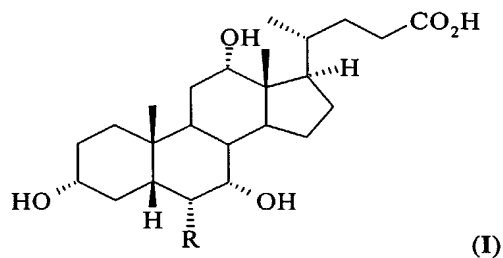
wherein R is ethyl, propyl or allyl.

Further aspects of the present invention are described in the following detailed description of the invention, examples, and claims.

10

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula (I):



wherein R is ethyl, propyl or allyl, and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

Suitable pharmaceutically acceptable salts according to the present invention will be readily determined by the skilled person and will include, for example, basic salts such as metallic salts with aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc or organic salts with N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Such salts may be prepared using conventional techniques, for example by reacting an appropriate base with a compound of Formula (I).

When used in medicine, the salts of the compounds of formula (I) should be pharmaceutically acceptable, but pharmaceutically unacceptable salts may conveniently be used to prepare the corresponding free base or pharmaceutically acceptable salts thereof.

As used herein, the term "solvate" is a crystal form containing the compound of formula (I) or a pharmaceutically acceptable salt thereof and either a stoichiometric or a non-stoichiometric amount of a solvent. Suitable solvents include for example water, methanol, ethanol, or acetic acid. Hereinafter, reference to a compound of formula (I) is to any physical form of that compound, unless a particular form, salt or solvate thereof is specified.

As used herein, the term "amino acid conjugates" refers to conjugates of the compounds of formula (I) with any suitable amino acid. Preferably, such suitable amino acid conjugates of the compounds of formula (I) will have the added advantage of enhanced stability in bile or intestinal fluids. Suitable amino acids include glycine and taurine. Thus, the present invention encompasses the glycine and taurine conjugates of any one of the compounds of formula (I).

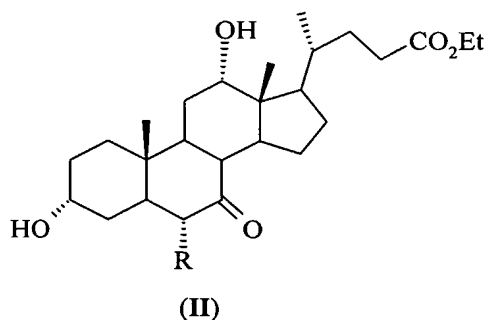
Preferred compounds of formula (I) include compounds selected from

the group consisting of 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-6 $\alpha$ -ethyl-5 $\beta$ -cholan-24-oic acid; 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-6 $\alpha$ -propyl-5 $\beta$ -cholan-24-oic acid and 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-6 $\alpha$ -allyl-5 $\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

- 5        The expression “compounds of formula (I)” refers hereinafter to compounds of formula (I) as described above and to pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

The compounds of the present invention can be prepared using a process comprising:

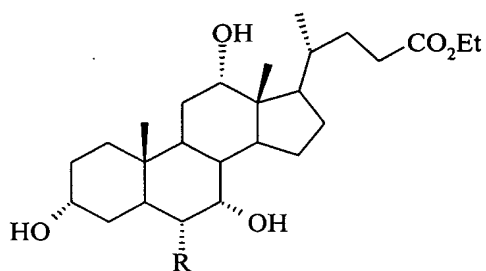
- 10    a)    reacting 3 $\alpha$ ,12 $\alpha$ -dihydroxy-7-keto-5 $\beta$ -cholan-24-oic acid with 3,4-dihydropyran to obtain 3 $\alpha$ ,12 $\alpha$ -ditetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid;
- b)    reacting 3 $\alpha$ ,12 $\alpha$ -ditetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid with an alkyl bromide of formula R-Br wherein R is ethyl, propyl or allyl to
- 15    obtain a compound of formula (II)



wherein R is ethyl, propyl or allyl;

- c)    reacting the compound of formula (II) with sodium borohydride to obtain a compound of formula (III)





(III)

; and

d) reacting the compound of formula (III) with sodium hydroxide to obtain a compound of formula (I).

5 More particularly, the compounds of formula (I) are prepared by reaction of the compounds of formula (III) with sodium hydroxide in a suitable solvent at room temperature. Suitable solvents comprise lower alcohols, such as ethanol. The reaction mixture can optionally be acidified with a suitable acid such as hydrochloric acid.

10 The compounds of formula (III) are conveniently prepared by reacting compounds of formula (II) with sodium borohydride in a suitable solvent at room temperature. Suitable solvents include lower alcohols such as ethanol.

The compounds of formula (II) are conveniently prepared by reacting 3 $\alpha$ ,12 $\alpha$ -tetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid with an alkyl  
15 bromide of the formula R-Br where R is ethyl, propyl or allyl in a suitable solvent and in the presence of n-butyl lithium and HMPA in diisopropylamine. Polar solvents such as tetrahydrofuran are preferred. Preferably, the reaction is carried out at low temperatures, such as about -70 to -80°C.

3 $\alpha$ ,12 $\alpha$ -Tetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid can be  
20 conveniently prepared by reacting 3 $\alpha$ ,12 $\alpha$ -hydroxy-7-keto-5 $\beta$ -cholan-24-oic acid with 3,4-dihydropyran in p-toluenesulfonic acid.

Pharmaceutically acceptable salts, solvates and amino acid conjugates of the compounds of formula (I) can be prepared from the free base according

to methods known to those skilled in the art.

The present invention also provides radiolabeled compounds of formula (I). Radiolabeled compounds of formula (I) can be prepared according to conventional techniques. For example, radiolabeled compounds of formula (I) can be prepared by reacting compounds of formula (I) with tritium gas in the presence of an appropriate catalyst. In one preferred embodiment, the compounds of formula (I) are tritiated.

Radiolabeled compounds of formula (I) are useful in assays for the identification of compounds which interact with FXR, such as those described in PCT Publication No. WO 00/37077 already incorporated herein.

The following examples further illustrate the invention.

Example: preparation of 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-6 $\alpha$ -ethyl-5 $\beta$ -cholan-24-oic acid

**a) 3 $\alpha$ ,7 $\alpha$ -Tetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid (2)**

p-Toluenesulfonic acid (6.0 g, 3.2 mmol) and 3,4-dihydro-2H-pyran (9.08 g, 108 mmol) were added to a solution of 3 $\alpha$ ,12 $\alpha$ -dihydroxy-7-keto-5 $\beta$ -cholan-24-oic acid (1) (5.8 g, 14.4 mmol) in 120 ml of dioxane. The reaction mixture was stirred at room temperature for 15 min and then was treated with methanol saturated with ammonia to pH of about 8-9. The solvents were evaporated under vacuum and the residue was extracted with chloroform (200 ml) and washed with a NaHCO<sub>3</sub> saturated solution (2 x 50 ml). After drying over dry Na<sub>2</sub>SO<sub>4</sub> and evaporation under vacuum, the residue was purified by silica gel chromatography. Elution with CHCl<sub>3</sub>:MeOH (90:10) afforded 5.9 g of compound 2 as a white solid (m.p.: 157-159°C).

**b) Ethyl 3 $\alpha$ ,12 $\alpha$ -dihydroxy-6 $\alpha$ -ethyl-7-keto-5 $\beta$ -cholan-24-oate (3).**

n-Butyl lithium (21.1 ml, 1.6 M in hexane) and HMPA (4.3 ml) were added dropwise at -78°C to a solution of diisopropylamine (4.1 ml, 33.7 mmol) in 250 ml of anhydrous THF. The mixture was kept at -78°C for further

mmol) in 250 ml of anhydrous THF. The mixture was kept at  $-78^{\circ}\text{C}$  for further 30 min, thereafter  $3\alpha,12\alpha$ -ditetrahydropyranyloxy-7-keto- $5\beta$ -cholan-24-oic acid (2) (6 g, 10.4 mmol), dissolved in 50 ml of anhydrous THF, was cooled to  $-78^{\circ}\text{C}$  and dropped into the mixture. After 20 minutes ethyl bromide (7.8 ml, 105 mmol) dissolved in THF (20 ml) was slowly added and the mixture was allowed to warm up to room temperature overnight. The solvents were evaporated under vacuum, acidified with 10% HCl, extracted with ethyl acetate (5 x 200 ml) and washed with a saturated NaCl solution (1 x 200 ml). After drying over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporation under vacuum, the crude residue was refluxed in a 2N HCl solution in EtOH (50 ml) for 12 hours. The mixture was evaporated under vacuum and extracted with ethyl acetate (300 ml), washed with a  $\text{NaHCO}_3$  saturated solution (2 x 100 ml), dried over  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum. The residue was purified by silica gel chromatography. Elution with petroleum ether:ethyl acetate (70:30) afforded 0.63 g of ethyl  $3\alpha,12\alpha$ -dihydroxy- $6\alpha$ -ethyl-7-keto- $5\beta$ -cholan-24-oate (3) as an amorphous solid.

**c) Ethyl  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -ethyl- $5\beta$ -cholan-24-oate (4).**

Ethyl  $3\alpha,12\alpha$ -dihydroxy- $6\alpha$ -ethyl-7-keto- $5\beta$ -cholan-24-oate (3) (0.185 g, 0.4 mmol) was dissolved in 30 ml of 96% EtOH and treated with  $\text{NaBH}_4$  (30 mg, 0.8 mmol). The mixture was stirred at room temperature for 2 hours, added with water (10 ml), partially concentrated under vacuum and extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with a saturated NaCl solution (1 x 50 ml), dried over  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum to give ethyl  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -ethyl- $5\beta$ -cholan-24-oate (4) (0.15 g) as a white solid (m.p.:  $55-57^{\circ}\text{C}$ ).

**d)  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -ethyl- $5\beta$ -cholan-24-oic acid (1).**

Ethyl  $3\alpha,7\alpha,12\alpha$ -trihydroxy- $6\alpha$ -ethyl- $5\beta$ -cholan-24-oate (4) (0.10 g, 0.22 mmol) was dissolved in 15 ml of 96% EtOH and added to a 10% NaOH

solution in 96% EtOH (2 ml, 5 mmol). The mixture was refluxed for 4 hours, then acidified with 3N HCl and extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with a saturated NaCl (1 x 50 ml) solution, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The residue was  
5 chromatographed over a silica gel column. Elution with CHCl<sub>3</sub>:MeOH (95:5) afforded 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-6 $\alpha$ -methyl-5 $\beta$ -cholan-24-oic acid (1) (0.042 g).

Preferably, the compounds of formula (I) are FXR agonists. As herein used, the term "agonist" refers to compounds which induce 50% FXR  
10 activation in comparison with CDCA, the positive control disclosed in WO 00/37077 published on 29 June 2000 to Glaxo Group Limited, herein entirely incorporated by reference. More preferably, the compounds of the invention induce 100% FXR activation in the proximity scintillation assay or in the HTRF assay as described in WO 00/37077.

15 The compounds of the formula (I) are useful for a variety of medicinal purposes. The compounds of formula (I) may be used in methods for the prevention or treatment of FXR-mediated diseases and conditions. FXR-mediated diseases or conditions include cardiovascular diseases including atherosclerosis, arteriosclerosis, hypercholesteremia, and hyperlipidemia. In  
20 particular, the compounds of formula (I) are useful for the treatment and prevention of cardiovascular diseases including atherosclerosis and hypercholesteremia. The compounds of formula (I) are also useful for increasing HDL-cholesterol and for lowering triglycerides.

In addition, the compounds of the present invention are useful for the  
25 prevention and treatment of cholestatic liver diseases. The compounds of the present invention increase the flow of bile acids. An increased flow of bile acids improves the flux of bile acids from the liver to the intestine. *See*, C. Sinal, *Cell* **102**: 731-744 (2000). Essentially, FXR null mice demonstrate that

lipid homeostasis by virtue of the regulation of enzymes and transporters critical to lipid catabolism and excretion. FXR therefore is an important target for the treatment of a number of cholestatic liver disease and other lipid related diseases and conditions.

5           The methods of the present invention are useful for the treatment of mammals in general and of humans in particular.

          The methods of the present invention comprise administering a therapeutically effective amount of a compound of formula (I). As used herein, the term "therapeutically effective amount" refers to an amount of a  
10   compound of formula (I) sufficient to achieve the claimed effect. Accordingly, a therapeutically effective amount of a compound of formula (I) used in the prevention or treatment of FXR-mediated diseases or conditions will be an amount sufficient to prevent or treat the FXR-mediated disease or condition. Similarly, a therapeutically effective amount of a compound of formula (I) for  
15   the prophylaxis or treatment of cholestatic liver diseases or for increasing bile flow will be an amount sufficient to increase bile flow to the intestine.

          The amount of a compound of formula (I) or pharmaceutically acceptable salt or solvate thereof required to achieve the desired biological effect will depend on a number of factors such as the intended use, the  
20   administration route, and the recipient, and will be ultimately at the discretion of the attendant physician or veterinarian. In general, a typical daily dose for the treatment of FXR-mediated diseases and conditions, for instance, ranges from about 0.01 mg/kg to about 100 mg/kg. This dose may be administered as a single- or multiple- dose units or as a continuous infusion. Similar dosages  
25   will be suitable for the treatment of other diseases, conditions and therapies including the prophylaxis and treatment of cholestatic liver diseases.

          Thus, in a further aspect the present invention provides pharmaceutical compositions comprising, as the active ingredient, a compound of formula (I)

or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one pharmaceutical carrier or diluent. These pharmaceutical compositions may be used in the prophylaxis and treatment of the aforementioned diseases or conditions and in cardiovascular therapies as  
5 mentioned above.

The carrier must be pharmaceutically acceptable and must be compatible with the other ingredients of the composition. The carrier may be a solid or liquid and is preferably formulated as a single-dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active  
10 ingredient. If desired, other physiologically active ingredients may also be incorporated.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular, or intravenous), rectal, topical including transdermal, intranasal and inhalation administration. Most  
15 suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or on the therapy and on the active compound but, if possible, oral administration is preferred for the prevention and treatment of FXR-mediated diseases and conditions.

Suitable formulations for oral administration may be provided as  
20 discrete units, such as tablets, capsules, cachets, lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Suitable formulations for sublingual or buccal administration include  
25 lozenges comprising the active compound and, typically a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatine and glycerine.

Suitable formulations for parenteral administration typically comprise

sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Additional formulations suitable for parenteral administration include formulations containing physiologically suitable co-  
5 solvents and/or complexing agents such as surfactants and cyclodextrins. Oil-in-water emulsions are also suitable formulations for parenteral formulations. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Suitable formulations for rectal administration are preferably provided  
10 as single-dose suppositories comprising the active ingredient in one or more solid carriers forming the suppository base, for example, cocoa butter.

Suitable formulations for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin,  
15 polyethyleneglycols, alcohols, and combinations thereof.

The formulations of the invention may be prepared by any suitable methods, typically by uniformly and intimately admixing the active compound with liquids or finely divided solid carriers or both, in the required proportions and then, if necessary, shaping the resulting mixture as desired.

20 For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of a powdered active ingredient and an inert liquid diluent.

25 Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers, or insufflators.

For pulmonary administration via the mouth, the particle size of the

powder or droplets typically ranges from 0.5 to 10  $\mu\text{m}$ , preferably from 1 to 5  $\mu\text{m}$ , to ensure delivery into the bronchial tree. For nasal administration, a particle size ranging from 10 to 500  $\mu\text{m}$  is preferred to ensure retention in the nasal cavity.

5           Metered dose inhalers are pressurised aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquefied propellant. These devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150  $\mu\text{l}$ , to produce a fine particle spray containing the active ingredient. Suitable  
10           propellants include chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, anti-oxidants and suitable flavouring agents.

15           Nebulisers are commercially available devices that transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice, or by means of ultrasonic agitation. Suitable formulations for use in nebulisers consist of the active ingredient in a liquid  
20           carrier and comprising up to 40% w/w of the formulation, preferably less than 20%w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives, if the formulation is not a sterile one, for example, methyl hydroxy-benzoate, anti-oxidants, flavouring  
25           agents, volatile oils, buffering agents and surfactants.

Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the



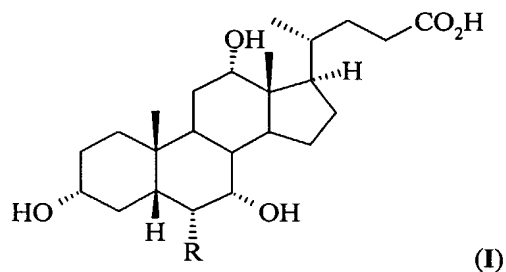
powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely  
5 of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation.

In addition to the ingredients specifically mentioned above, the formulations of the present invention may include other agents known to those  
10 skilled in the art of pharmacy, having regard for the type of formulation in issue. For example, formulations suitable for oral administration may include flavouring agents and formulations suitable for intranasal administration may include perfumes.

Therefore, according to a further aspect of the present invention, there  
15 is provided the use of a compound of formula (I) in the preparation of a medicament for the prevention or treatment of FXR-mediated diseases or conditions.

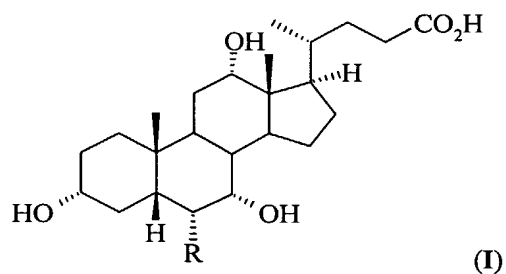
## CLAIMS

1. A compound of formula I:



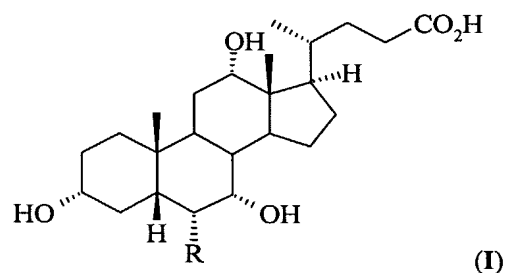
wherein R is ethyl, propyl or allyl, and pharmaceutically acceptable salts, solvates and amino acid conjugates thereof.

2. 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -Trihydroxy-6 $\alpha$ -ethyl-5 $\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates and amino acid conjugates thereof.
3. 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -Trihydroxy-6 $\alpha$ -propyl-5 $\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates and amino acid conjugates thereof.
4. 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -Trihydroxy-6 $\alpha$ -allyl-5 $\beta$ -cholan-24-oic acid and pharmaceutically acceptable salts, solvates and amino acid conjugates thereof.
5. The glycine conjugate of a compound of formula (I) :



wherein R is ethyl, propyl or allyl.

6. The taurine conjugate of a compound of formula (I):



wherein R is ethyl, propyl or allyl.

7. A compound as claimed in claim 1, wherein said compound is a FXR agonist.
8. A pharmaceutical composition comprising a compound as claimed in  
5 claim 1 and a pharmaceutically acceptable carrier or diluent.
9. A method for the prevention or treatment of a FXR-mediated disease or condition comprising the administration of a therapeutically effective amount of a compound as claimed in claim 1.
10. A method for the prevention or treatment of cardiovascular diseases  
10 comprising the administration of a therapeutically effective amount of a compound as claimed in claim 1.
11. A method as claimed in claim 10, wherein said cardiovascular disease is atherosclerosis.
12. A method for increasing HDL cholesterol, said method comprising the  
15 administration of a therapeutically effective amount of a compound as claimed in claim 1.
13. A method for lowering triglycerids, said method comprising the administration of a therapeutically effective amount of a compound as claimed in claim 1.
- 20 14. A method for the prevention or treatment of colestatic hepatic diseases comprising the administration of a therapeutically effective amount of a compound as claimed in claim 1.
15. A radiolabelled compound as claimed in claim 1.
16. The compound of claim 15, in which said compound is tritiated.
- 25 17. Use of a compound as claimed in claim 1 for the preparation of a medicament for the prevention or treatment of a FXR-mediated disease or condition.
18. Use of a compound as claimed in claim 1 for the preparation of a

medicament for the prevention or treatment of cardiovascular diseases.

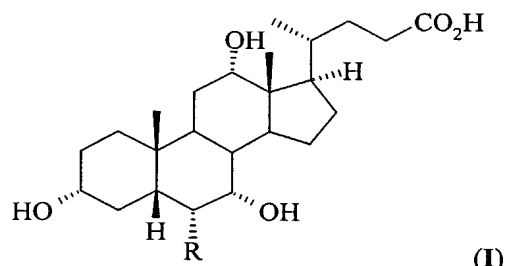
19. Use of a compound as claimed in claim 1 for the preparation of a medicament for the prevention or treatment of atherosclerosis.

20. Use of a compound as claimed in claim 1 for the preparation of a medicament for increasing HDL cholesterol.

21. Use of a compound as claimed in claim 1 for the preparation of a medicament for lowering triglycerids.

22. Use of a compound as claimed in claim 1 for the preparation of a medicament for the prevention or treatment of colestatic hepatic diseases.

23. A process for the preparation a compound of formula (I):

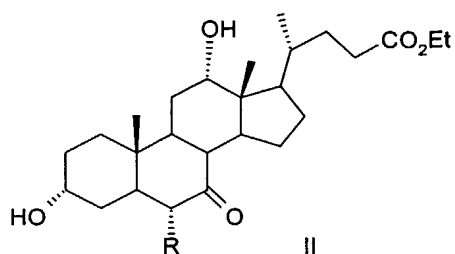


wherein R is ethyl, propyl or allyl, and pharmaceutically acceptable salts, solvates and amino acid conjugates thereof,

said process comprising:

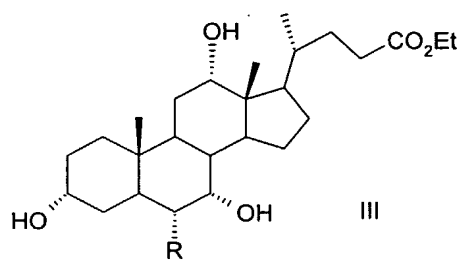
a) reacting 3 $\alpha$ ,12 $\alpha$ -dihydroxy-7-keto-5 $\beta$ -cholan-24-oic acid with 3,4-dihydropyran to obtain acid 3 $\alpha$ ,12 $\alpha$ -ditetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic;

b) reacting 3 $\alpha$ ,12 $\alpha$ -ditetrahydropyranyloxy-7-keto-5 $\beta$ -cholan-24-oic acid with an alkyl bromide of formula R-Br wherein R is ethyl, propyl or allyl to obtain a compound of formula (II)



wherein R is ethyl, propyl or allyl;

- c) reacting the compound of formula (II) with sodium borohydride to  
5 obtain a compound of formula (III)



; and

- d) reacting the compound of formula (III) with sodium hydroxide to  
obtain the compound of formula (I).